The Electronic Medication Complete Communication (EMC²) Study: Rationale and Methods for a Randomized Controlled Trial of a Strategy to Promote Medication Safety in Ambulatory Care

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Abstract

Background—Adverse drug events (ADEs) affect millions of patients annually and place a significant burden on the healthcare system. The Food and Drug Administration (FDA) has developed patient safety information for high-risk medications that pose serious public health concerns. However, there are currently few assurances that patients receive this information or are able to identify or respond correctly to ADEs.

Objective—To compare the effectiveness of the Electronic Medication Complete Communication (EMC²) Strategy to promote safe medication use and reporting of ADEs in comparison to usual care.

Methods—The automated EMC² Strategy consists of: 1) provider alerts to counsel patients on medication risks, 2) the delivery of patient-friendly medication information via the electronic health record, and 3) an automated telephone assessment to identify potential medication concerns

or ADEs. The study will take place in two community health centers in Chicago, IL. Adult, English or Spanish-speaking patients (N=1,200) who have been prescribed a high-risk medication will be enrolled and randomized to the intervention arm or usual care based upon practice location. The primary outcomes of the study are medication knowledge, proper medication use, and reporting of ADEs; these will be measured at baseline, **4** weeks, and three months. Intervention fidelity as well as barriers and costs of implementation will be evaluated.

Conclusions—The EMC[2] Strategy automates a patient-friendly risk communication and surveillance process to promote safe medication use while minimizing clinic burden. This trial seeks to evaluate the effectiveness and feasibility of this strategy in comparison to usual care.

Keywords

medication safety; health literacy; adherence

INTRODUCTION

Research has repeatedly demonstrated that patients lack essential information on how to safely take prescribed (R_x) medications.[1,2] This lack of knowledge has been cited as a root cause of unintentional misuse and medication errors, which can lead to serious adverse drug events (ADEs).[2,3] While the exact prevalence of medication errors and ADEs in ambulatory care is difficult to determine, nearly 4.5 million outpatient physician visits and 1 million emergency department admissions are attributed to ADEs annually.[4,5] Estimates also indicate that among adults who take a medication and are seen in outpatient practices, up to 25% experience an ADE over the course of a year.[5,6]

While most prescribed medications carry risks, approximately 400 drugs have been deemed by the Food and Drug Administration (FDA) to possess serious public health concerns, warranting a Risk Evaluation and Mitigation Strategy (REMS).[7] Yet, few, if any, mechanisms exist to ensure and confirm that primary care patients receive and understand instructions for use, risk information, or instructions on proper actions to take in response to ADEs. Routine monitoring for the safety of patients who use higher-risk medications is also not presently possible. Instead, providers rely heavily upon patients to independently learn about their prescribed medication, identify ADEs, and seek medical support.[6] Thus ADEs are often detected late, if at all, leaving patients at risk for further harm and less effective treatment. From a public health perspective, a more comprehensive method for detecting ADEs could provide new information on a medication's safety profile and inform the care of others who are also taking the medication.

To address these shortcomings, we developed the Electronic Medication Complete Communication (EMC[2]) Strategy, which seeks to 'hardwire' risk communication and surveillance of higher risk medications in primary care using health information technologies, specifically electronic health record (EHR) and interactive voice recognition (IVR) technology. Herein we provide an overview of the EMC[2] Strategy and describe the methods and rationale for evaluating this approach in a randomized controlled trial (RCT) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

METHODS

The EMC^2 Strategy

The EMC^2 Strategy consists of several components designed to promote: 1) provider counseling on medication use, risks and benefits; 2) dissemination of understandable, actionable medication information to patients; and, 3) routine surveillance of medication use and risks in ambulatory care. To automate implementation and limit use of clinic resources, the EMC^2 intervention takes advantage of EHR and IVR platforms to facilitate patient education and medication monitoring. Specifically, patients enrolled at an intervention site will be exposed to the EMC^2 Strategy, which is comprised of the following key components (Figure 1):

1. Provider Medication Alert—When a provider places a new order or dose change for an existing prescription for a high-risk medication, an EHR-generated alert will notify the provider that the medication requires patient counseling. This alert will contain a brief description of the key risks or side effects that patients may experience while taking this medication; this information is directly derived from the FDA-approved Medication Guide for the medication. Providers will also be given the option of clicking on an html link within the alert to view the entire text of the Medication Guide if desired.

2. Automated Delivery of FDA Medication Guide + Summary—The medication order will automatically cue printing of: 1) the FDA-approved Medication Guide for the drug in question and 2) a 1-page, patient-friendly summary of the Guide (i.e. Medication Guide Summaries). These materials will be provided to patients with the After Visit Summary following the provider encounter. FDA Medication Guides are required to be distributed for the medications selected for this study at the point of dispensing; however, prior research indicates that pharmacies often fail to provide patients with this information.[8] To ensure that patients receive this essential information, it will be automatically printed and distributed to patients at the point of prescribing in primary care. Medication Guide Summaries were developed by our research team using health literacy 'best practices' to promote patient understanding of medication risks and instructions for use. A prior study conducted among 1,003 patients found that the Medication Guide Summaries significantly improved patients' ability to retrieve and apply medication information.[9]

3. IVR Follow-Up Phone Assessment—Within **14 days** after enrollment in the study, patients will receive a text message asking them to contact an automated telephone system. Calling this line will initiate an IVR call, which will last less than 5 minutes and asks patients to report whether they have: a) filled the prescription, b) are taking the medication, and c) have experienced side effects that are unique to the medication in question. The system also explores barriers to obtaining the medication for patients who had not yet done so and barriers to adherence for patients who report non-adherence. A second IVR call will be placed **4 weeks** later to follow up with patients again, using a similar format and series of questions. Automated conversation systems have been used previously by members of our study team to improve clinical screening, counseling, and medication management.[10]

4. Clinic Follow-up—The results of the IVR telephone assessment will be sent back to the EHR as patient-reported data in the form of a laboratory report. It will be routed to the prescriber of the high-risk medication for which the surveillance is being conducted. In the event that a serious concern is identified, the nature of the issue (e.g., non-adherence, patient-reported side effect, etc.) will be detailed in this report. Clinic staff will monitor reports and respond to any identified concerns by calling and counseling the patient. Clinics have tailored their protocol for responding to reports based upon the resources, needs, and staffing of the individual clinics.

Study Design and Aims

To evaluate the impact and scalability of the EMC^2 Strategy, we are conducting a 2-arm RCT. The specific aims of this three-year trial are to: 1) test the effectiveness of the EMC^2 Strategy, compared to usual care, to improve a) patient understanding of medication risks, b) patient use of higher-risk R_x medications, and c) the detection of ADEs; 2) assess whether the EMC^2 Strategy can reduce disparities in medication understanding and use by patient literacy level, English proficiency, and age compared to usual care; and, 3) evaluate the fidelity of the EMC^2 Strategy to promote provider counseling, deliver patient R_x information, monitor understanding and use, and inform providers of potential harms. In addition to evaluating the effectiveness of the EMC^2 Strategy, we will also: 1) explore patient, provider, and health system barriers to implementing the EMC^2 Strategy, and 2) determine the cost of delivering the EMC^2 Strategy in primary care from a health system perspective.

Setting

Study sites for this trial include two Federally Qualified Health Centers (FQHCs) affiliated with The Alliance, an EHR system user-community composed of safety net providers. The Alliance is an innovator and national leader in using health information technology among FQHCs. For this study, we are working specifically with Heartland Health Centers and Near North Health Centers; both are located in metropolitan Chicago and are Public Health Service 330-funded FQHCs with federal mandates to care for medically underserved areas. Patients are racially and ethnically diverse; most are low income. Study clinics share a common EHR platform (GE Centricity®), which is centrally hosted by The Alliance.

Study Medications

To select the higher-risk medications targeted for this study, we first identified which drugs requiring an FDA Medication Guide were most commonly prescribed at Alliance-affiliated clinics. As the EMC^2 Strategy is designed to support patient adherence and continued safe use of higher risk medications in an ambulatory care setting, we then removed any medications that were poorly matched for the approach, for example, those that are available without a prescription, primarily prescribed 'as needed' (PRN), for short-term use only, or are administered directly to patients in a clinic. A total of 69 medications were selected for the study.

Participants

We will recruit 1,200 patients from participating clinics into the study; recruitment is anticipated to begin in December 2016 and will continue for approximately two years. Eligibility criteria for the study includes: 1) age 21 years and older; 2) English or Spanish speaking; 3) self-reported responsibility for administering one's own medication; 4) having received a new or changed dose prescription for a study medication at the index clinic visit; and, 5) having one's own telephone or cell phone. Patients will be excluded if they have any severe, uncorrectable vision, hearing or cognitive impairments that would preclude study participation or consent.

The sample size for this study was based on comparisons of the primary outcome of medication knowledge between the two arms (i.e., usual care vs EMC2) at the 3-month interview. We expect participants in the usual care arm to score an average of 55.6 (SD=28.4) based on a previous study testing comprehension of the FDA standard Med Guides to those to be used in this study.[9] Enrolling 1200 participants and estimating 80% retention at the in-person follow-up interview (n=960, 480 per arm), we will have 80% to detect a minimum difference of 5.5 between the EMC2 and the usual care arm assuming a Type I error of 5%, assuming 100 patients per practice site enrolled at baseline and n=80 available at 3 month follow-up. This effect size was calculated based on an independent t-test with a variance inflation factor to account for the cluster randomized design. An intra-class correlation coefficient (ICC) of 0.001 was used as we expect the clustering of practice site to have minimal influence on patient outcomes.

Randomization

As the EMC^2 Strategy includes changes to healthcare delivery, the intervention itself is diffuse and patient randomization is not feasible. Therefore, randomization will occur at the practice location level. There are 12 practice locations affiliated with the two study community health centers; participating practice locations will be matched by patient volume and proportion of Spanish speakers at each location and one from each pair will be randomly assigned 1:1 to either intervention or control arms using a random number generator. All patients attending a practice location will subsequently be randomized to either intervention or control arms based upon the assignment of the practice that they attend for medical care. As such, blinding will not be possible.

As practice locations are randomized to either intervention or control arms, all patients (i.e., both study participants and non-participants) who visit an intervention clinic and receive a prescription for one of the study medications will automatically receive some EMC^2 components during their clinic visit (provider medication alert, Medication Guide + Summary). However, only those patients who then consent to participate in the study will be eligible to receive the remaining EMC^2 components (IVR assessment, clinic follow-up) and to participate in evaluation activities. This randomization and recruitment process will ensure that recruited patients receive all in-clinic EMC^2 components on the day they receive a new or changed dose prescription for a higher risk medication. It will also result in a trickle down of some components of the EMC^2 Strategy being given to patients seen at an intervention practice site, but not enrolled in the study.

Patients attending a usual care clinic will receive standard care. This is likely to include variable rates of physician counseling on medication safety and use and little, if any, follow-up post-visit. Patients will also not receive a Medication Guide Summary or FDA-approved Medication Guide at the point of prescribing; however, by law they should receive the latter at the pharmacy at the point of dispensing.

Human Subjects Protection and Clinical Trial Registration

The Institutional Review Board (IRB) of Northwestern University, Boston University and participating community health centers approved all study procedures. The clinical trial is registered on clinicaltrials.gov [NCT02785458].

Recruitment and Data Collection

On a nightly basis, Research Assistants (RAs) at Northwestern University will electronically receive, via a secure platform, a list of patients who were prescribed a study medication that day at a participating community health center. RAs will call patients and invite them to participate in the EMC^2 evaluation. After confirming patient eligibility and obtaining verbal consent, the RA will administer the baseline interview over the phone. Additional phone interviews will be conducted by RAs at approximately 4 weeks and 3 months post baseline to capture study outcomes. Study data will be collected and managed using REDCap electronic data capture tools hosted by the Northwestern University Clinical and Translational Sciences (NUCATS) Institute.[11]

Measurement

Patient outcomes include: 1) knowledge of an R_x medication's benefits and risks; 2) medication use (proper use, medication adherence); and, 3) reporting of ADEs. We will also collect data on literacy level, English proficiency, and age. Additionally, we will examine: 4) fidelity outcomes that assess how reliably intervention components were delivered and received by patients, and 5) the costs of the intervention.

Medication Knowledge—Medication-specific knowledge measures have been created for each high-risk medication. Similar items are standard across medications, related to general use, risks and benefits, and side effects. Correct answers are tailored to the available content included in each Med Guide Summary, as done previously by our team.[12] Medication knowledge will be assessed at baseline, 4 weeks and 3 months.

Medication Use—We will assess medication use by three domains: fill, proper use, and adherence. *Fill* will be assessed by patient self-report (yes/no) of having obtained the medication from the pharmacy. *Proper Use* (yes/no) will be assessed by asking patients to report the correct dose (amount of medication taken each time), frequency (times per day), and total amount per day taken for each high risk medication prescribed; all must be answered correctly for it to be considered proper use. Finally, adherence will be measured as the self-reported number of missed doses within the past 4 days and via a telephone-based pill count using established guidelines (pill form medications only).[13] Medication use will be assessed, where applicable, at baseline, **4 weeks** and 3 months.

Reporting of ADEs—During the 3-month interview, patients will be asked to report if they have experienced any side effects from their medication since it was prescribed (yes/no). If they respond yes, they will be asked to provide details on the side effect experienced. Two pharmacists will independently review all self-reported side effects to determine whether these symptoms could reasonably be linked to one of the prescribed high-risk medications. Subsequently, patients will be asked a series of targeted questions to determine if they experienced any side effects specifically identified on the FDA Medication Guide as being associated with the medication in question. We will then ask patients whether side effects were reported to their healthcare provider (yes/no) or resulted in a clinic visit, emergency room visit or hospitalization (yes/no). When possible, RAs will review medical records to determine if reported side effects and/or events were documented in the patient's chart.

In addition to investigating the effectiveness of the intervention, we will also evaluate the fidelity of the EMC^2 Strategy to promote provider counseling, deliver patient R_x information, monitor understanding and use, and inform providers of potential harms. During the baseline interview (1-3 days post index clinic visit), we will ask patients (yes/no) whether a provider counseled them on the medication purpose, risk, and benefit. We will also ask the Health Literacy supplemental items of the Consumer Assessment of Health Providers Survey (CAHPS) to evaluate the extent and quality of provider verbal counseling on R_x medications.[14] At baseline, we will also collect EHR data to determine whether the Med Guide Summary and FDA Medication Guide were printed along with intervention patients' after-visit summaries and will ask patients in both arms to report whether they received any written medication information from their provider. Finally, at 3 months post baseline, we will collect data from the IVR system and EHR to determine whether IVR calls were completed by patients, whether responses warranted clinic follow-up and counseling, and whether this follow-up was received by patients.

Post-trial, qualitative interviews and/or discussion groups with providers, clinic staff, and patients will explore patient, provider, and health system barriers to implementing the EMC^2 Strategy. We will also assess the financial costs of running the EMC^2 Strategy, including printing (printer ink, paper, staff time) and programmer time to develop and maintain the EHR and IVR platforms, to determine the cost of delivering the EMC^2 Strategy in primary care from a health system perspective.

Data Analysis Plan

The proposed trial uses a cluster-randomized design where the practice location is the unit of randomization. We will randomize 12 locations to two arms (usual care, EMC2) resulting in 6 per arm. Locations will be matched by total number of patients eligible for the study as well as proportion of Spanish speaking patients, with one location from each pair randomized to each arm. We will accrue ~100 patients per location, on average, and conservatively anticipate 80% retention at 3-month follow-up. These estimates result in 1200 participants recruited with an anticipated 960 patients (480 per arm, 80 per location) available for primary data analysis.

Medication knowledge associated with high risk medications is the first primary outcome of interest for Aim 1, and will be analyzed as a score ranging from 0-100 reflecting the percent of items correct for each medication. Medication use outcomes (proper use, adherence) and detection of ADEs are secondary outcomes of interest. Associations between the outcomes and potential confounders at the patient (socio-demographic characteristics, comorbidities, # and type of medications taken, previous history with side effects, literacy, and primary language) and medication (drug type, route of administration) levels will be examined. We intend to use generalized linear mixed models (GLMM) to analyze the data, which can handle data that is missing at random (MAR). Additionally, we will examine rates of missing data, and determine if there are any discernible patterns using GLMMs with a logit link function to predict the presence of missing data. Should we find significant predictors, we will use multiple impute methods and present results as secondary analyses.

To account for the correlated nature of the data from participants at the same practice and multiple observations per patient, we will use GLMMs for analyses of all data, specifying identity link for continuous and the logit link for binary outcomes using PROC GLIMMIX in SAS (v.9.4). Treatment assignment by time will be the independent variable of primary interest and modeled as a fixed effect and practice location as a random effect, with additional subject statement to model correlations within patient. We will also include fixed effects for any potential confounding covariates noted in the descriptive studies. For all GLMM analyses we will report point estimates and 95% confidence intervals, and the extent to which random effects suggest correlation of outcomes within practice location. Additionally, we will estimate the ICCs for all outcomes to be used in future studies.

For Aim 2, we will repeat all GLMM analyses described above, but with the inclusion of a fixed effect for participants' literacy defined as limited vs. adequate. We will formally test for differences in intervention effects according to literacy by including a literacy-intervention interaction term. Statistically significant interaction terms ($p<0.05$) will indicate that the disparities in understanding between the intervention and usual care group vary by literacy level. Similar analyses will be used to test for interactions of intervention effects by age and English proficiency.

Following completion of enrollment, we will determine the extent to which the intervention was implemented as planned in the intervention arm. We ask patients whether they received the Med Guide Summaries and the post-visit IVR calls and will inquire about provider counseling on medication use and benefits. Since counseling behaviors and receipt of educational materials will be assessed in both arms, we will be able to determine whether our intervention promoted provider counseling and delivery of patient Rx information using t-tests, Wilcoxon Rank-Sum, or χ2 tests, as appropriate.

A combination of patient focus groups and individual interviews with prescribers and nurses will be conducted to understand in detail any barriers to implementation of the EMC2 Strategy. Preliminary findings from fidelity analyses highlighting process outcomes and possible 'voltage drops' in implementation will be explored further in these interviews. Our conceptual framework will guide discussions and interviews, along with Normalization Process Theory (NPT).[15-17] NPT follows sociological principles pertaining to the

implementation of innovations into practice. It takes the worldview that multifaceted interventions are often needed, and that implementation and integration often depends on: the work (tasks to be completed), who is responsible, how it impacts current practice and is understood by an organization. Suggestions for further improvement of the strategy will be solicited. Discussions will be audio-recorded and transcribed for thematic analyses.[18] Responses will be organized and summarized by provider/patient and component.

We will directly measure and assess the provider perspective costs of developing and running the EMC2 Strategy. Specifically, we will estimate the incremental cost of the intervention relative to usual care from the perspective of the Alliance and each FQHC implementing this process and tools. The primary costs of running the EMC2 Strategy involves the limited expenses around printing (printer ink, paper, staff time) as a result of generating new medication information with after-visit summaries. However, we will include estimates for minimal programming maintenance, for both GE Centricity EHR and the IVR system, and will test the sensitivity of results to changes in the maintenance requirements in terms of programmer hours. We also will separately track development costs for software and other programming requirements based on programmer hours. Staff/programmer costs will be measured using tracked time spent on the intervention and wage estimates. We will test the sensitivity of operational costs to different assumptions about the potential use of variable staff using different salaries but assuming the same proficiency in terms of time required. Further, we will assess the sensitivity of estimates to different proficiency levels that could arise from learning by doing.

DISCUSSION

A risk communication and surveillance strategy is needed in primary care to ensure that patients are adequately informed about medication risks and are taking medications safely. To date, most initiatives to reduce ADEs have focused exclusively on physician prescribing practices.[19] Yet most ADEs do not result from poor prescribing decisions, but from side effects experienced from an appropriately prescribed drug.[19] As many as half of ADEs can be detected and mitigated at an early stage, making opportunities for amelioration up to 2.5 times as likely as opportunities to prevent ADEs through better prescribing.[6,19,20]

The EMC[2] Strategy was devised to leverage EHR and IVR technologies to: 1) prompt and guide provider counseling; 2) automate the delivery of Medication Guides and patient-friendly medication information at prescribing; 3) engage patients post-visit to confirm that they have sufficient information and are using medications properly; and, 4) activate the clinical team to help patients overcome any barriers to safe medication use. Overall, the strategy should enhance patient education on risks and benefits of medications and provide better opportunities for monitoring patient medication use in ambulatory care. As 37% of ameliorable ADEs have been attributed to patients not informing their provider of signs and symptoms, providing more opportunities for patients to report potential ADEs to providers is a crucial first step towards promoting medication safety.[6,19]

There are strengths and limitations to this study that should be noted. While multiple practice locations and community health centers are serving as sites for the study, all are

located in the Chicago metropolitan area. Results may not be generalizable to rural populations or those living in different geographic regions. Additionally, many study outcomes, such as medication adherence and ADEs, are difficult to measure. This study will rely upon patient self-report for these outcomes, which is subject to recall bias. Validated scales and measures are being used to minimize this concern. In terms of strengths of the study, we are testing the EMC^2 intervention in resource-constrained FQHCs among 1,200 English and Spanish-speaking patients; this will help determine the feasibility of implementing the strategy in other community health clinics for low-income, diverse patient populations. This study is also strengthened by our post-trial investigations, which will explore the barriers and facilitators to implementing the EMC^2 Strategy and will also help determine its cost-effectiveness. These factors are often not assessed in randomized controlled trials and can be vital to dissemination and implementation efforts, should the intervention be shown to be effective.[21]

ADEs affect millions of patients each year and place a significant burden on the U.S. healthcare system.[4,20] A risk communication and surveillance strategy is needed to assure that patients obtain their medications, know how to take their medications, can identify and properly respond to ADEs, and are given a chance to communicate this information to providers. This study aims to 'hardwire' this process into normal clinical practice through provider reminders to counsel on high-risk medications, patient-friendly medication information, automated follow-up phone assessments, and activation of the clinical team to address medication issues. If proven effective, the EMC^2 Strategy could be implemented across the nation–including clinics with limited resources that treat vulnerable patient populations–to support the safe use of high-risk medications in ambulatory care.

Acknowledgments

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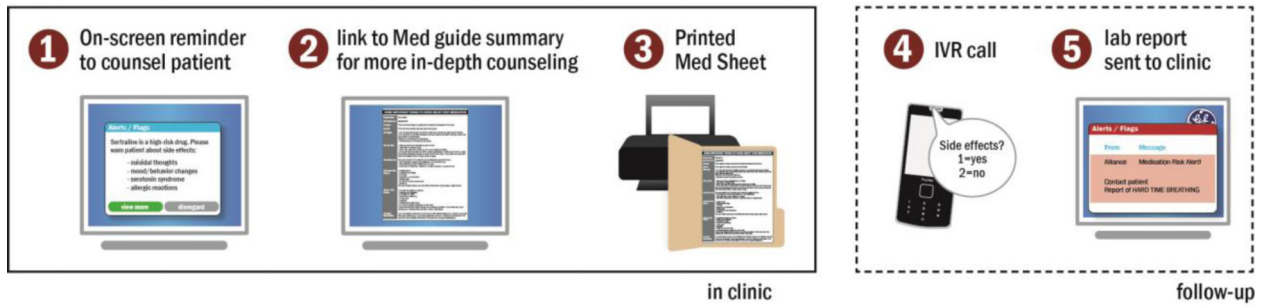
Figure 1.
Sequence of EMC^2 Components